## REMARKS

Claims 1-53 are now pending in the application, new claims 22-53 having been added by the above amendment. Claims 11, 12, 15, 16, and 18-21 are withdrawn from prosecution as drawn to non-elected inventions. The amended and new claims are supported throughout the application as filed, e.g., at p.2, lines 8-11 and lines 25-27; p.3, line 9 and lines 26-31; p.4, lines 12-19 and lines 23-29; p.5, lines 6-11 and lines 25-28; p.6, lines 16-30; p.7 lines 13-26; p. 8, lines 4-5; p.10, lines 8-10; p.12 lines 11-14; p.20, lines 26-30; p.21, line 1 and lines 9-14; p.23, line 22-p.24, line 3; and p.32, lines 9-14. No new matter has been added.

All examined claims were rejected on one or more grounds as discussed below.

**Telephone Conference and Supplemental Office Action Response of March 25, 2004**

Applicants would like to thank Examiner Andres for taking the time to conduct a telephone conference with Applicants' representative, Marcos Rivas, on March 22, 2004, and issuing a Supplemental Office Action on March 25, 2004. During the telephone conference, Applicants' representative informed the Examiner that his files were missing the sequence alignment cited on page 7 of the Office Action paper of October 23, 2003, and that he believed the alignment had not been mailed with the Office Action on October 23, 2003. He also questioned the basis for the statement at page 2 of the original office action concerning the priority date to which the claims are entitled. The Examiner kindly agreed to forward the sequence alignment by facsimile, and further agreed to issue a Supplemental Office Action, enclosing the sequence alignment, reformulating the paragraph concerning priority, and restarting the period for response. That Supplemental Office Action was duly mailed to Applicants on March 25, 2004.

On March 29, 2004, Applicants' representative found the original sequence alignment mailed with the Office Action of October 23, 2003. The sequence alignment had been misplaced. Applicants' representative would like to apologize for the confusion that led the Examiner to issue the Supplemental Office Action.

Applicants note that the present response is being filed before the final deadline for response set by the October 23, 2003, office action. If the Examiner believes that the reformulation of the basis for denying priority, taken alone, is insufficient justification for restarting the period of response, she is asked to charge Deposit Account 06-1050 for the entire amount of the extension fee due for extensions to April 23, 2004.

**Specification**

As per the Examiner's request, trademarks have been amended to be capitalized and appropriately notated throughout the application.

**Priority**

Applicants respectfully disagree with the Examiner's assertion that the priority documents submitted for this case do not disclose a utility and are therefore not enabled. Applicants present ample reasons below why the currently claimed subject matter, and therefore the priority documents that support this subject matter, meet the statutory requirements of both 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully request acknowledgement that the present application is entitled to the priority dates of International Patent Application No. PCT/JP00/06050 and Japanese Application No. 11-252190, filed on September 6, 2000, and September 6, 1999, respectively.

**35 U.S.C. § 101**

Claims 1-10, 13, 14, and 17 stand rejected for allegedly lacking a substantial, specific, and credible utility or a well-established utility. The present amendment transfers the subject matter of original claim 1, parts (b)-(e), to new claims 43-46, respectively. Applicants respectfully traverse this rejection as it may apply to all claims as amended.

Applicants submit that the present application clearly identifies the following specific, substantial, and credible "real world" uses for the claimed nucleic acids and polypeptides:

i) They are useful as tools "for purifying and cloning proteins related to hematopoietic stem cell formation, [and] bone formation" (p.3, line 31- p.4, line 3; see also p.2, lines 13-15, and p.32, lines 9-12).

ii) They are useful for "screening drug candidate compounds as therapeutic agents for immune and hematopoietic system-related diseases, bone formation-related diseases" (p.4, lines 2-3).

iii) They are useful for promoting the activity of BMP2/4 by binding BMP2/4 (see, e.g., p.3, lines 27-28, and p.4, lines 27-29).

iv) They are useful for the study of embryonic development, specifically for the "elucidation of mechanisms of differentiation and bone formation associated with hematopoietic stem cell generation" (p.32, lines 9-13).

v) The polypeptides can be used as antigens to generate antibodies that are useful to detect, measure, or purify TSG-like protein(s) (p. 16-20).

vi) The nucleic acids are useful as probes to study the expression patterns of TSG-like protein. An example of such a probe is a nucleic acid comprising at least 15 nucleotides that hybridizes to the DNA (SEQ ID NO:1) encoding the protein described in SEQ ID NO:2 or to a complementary strand thereof (p. 20, lines 29-31; see also Example 3, p.32, lines 1-5).

vii) The nucleic acids can be used to generate fusion proteins that are useful in a number of the methods disclosed above (p.5, line 27-p.6, line 10).

According to the Utility Examination Guidelines, a utility rejection is not appropriate where Applicants have asserted any specific and substantial utility that is credible. "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." Federal Register Notices, 66(4): 1098 (2001) (Utility Examination Guidelines). The Office Action does not adequately explain how Applicants' asserted utilities are not specific, substantial, and credible.

The utilities asserted by Applicants are clearly not insubstantial, non-specific, or "throw-away" utilities such as the use of claimed subject matter as landfill. See Utility Examination Guidelines p. 1098. Nor are these utilities analogous to the utter lack of disclosed utility in Brenner v. Manson, 148 U.S.P.Q. 689 (1966), cited by the Examiner. Manson concerned product-by-process claims for making a compound for which no utility whatsoever was disclosed. The Manson facts are thus readily distinguishable from the present invention, because the present Applicants have disclosed a number of utilities for both the disclosed nucleic acids and encoded proteins (as detailed above).

The many disclosed utilities (see i)–v) above) are explicitly related to both therapeutics and research tools that are useful in the treatment and study of specific conditions, i.e., conditions of the immune system, hematopoietic system-related diseases, and bone formation-related diseases. These are not "general utilities" that could be asserted for any and every nucleic acid or protein.

The Office Action objects to the absence of "objective evidence of any activity for the encoded protein or to show that the protein even exists." Office Action paper, p. 3. As explained in more detail below, however, requiring "objective evidence" from Applicants is not the legal standard imposed by 35 U.S.C. §101. To the contrary, it is incumbent on the Examiner to provide an objective basis for doubting the assertions made in the specification, which otherwise must be taken as true. No such objective basis has been put forward. Therefore,

Applicants respectfully submit that they do not need to submit "objective evidence" of the protein's activity.

Furthermore, Applicants do not begin to understand why the Examiner appears to demand objective evidence for the claimed protein's existence. This might be an issue if Applicants were basing their claim on nothing but a genomic sequence with an open reading frame that encoded a hypothetical protein, but that is certainly not the case here. First, the disclosed nucleotide sequence (SEQ ID NO:1) is a cDNA sequence obtained by screening an embryonic cDNA library, so the sequence plainly represents an actual mRNA expressed in embryonic cells. Second, Applicants demonstrated by Northern hybridization experiments that the mRNA is in fact expressed in several mouse tissues. See, e.g., p.32, lines 1-5, of the specification. Third, the specification notes the homology of the SEQ ID NO:2 protein to the *Drosophila* TSG protein, which has been extensively studied and shown to "exist". All told, one of ordinary skill in the art would understand from reading the specification that the encoded protein "exists". The Office Action provides no evidence, nor even a theoretical basis, to doubt the existence of the protein. Even if such evidence were put forward by the Examiner, it would be overcome by the post-filing date references submitted herewith and cited on the enclosed Form PTO-1449: (Ref AE) Nosaka et al., Mol. Cell Biol. 23:2969-2980 (2003), (Ref AF) Graf et al., Mammalian Genome 12:554-560 (2001), and (Ref. AG) Chang et al., Nature 410:483-487 (2001), concerning TSG knock-out mice, the developmental expression of the TSG protein, and use of the TSG gene to study embryonic BMP signaling, respectively.

Applicants have asserted five utilities (see i)- v) above), each of which is specific, substantial, and credible. Any one of these would be sufficient to meet the utility requirement. It is improper to discount any of these asserted utilities without evidence that a person of ordinary skill in the art would question the credibility of the asserted utility. The Revised Interim Utility Guidelines Training Manual (Utility Manual), states that an asserted utility "is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion." Utility Manual p.5. The Office Action does not expose "a serious flaw" (nor **any** flaw for that matter) in the logic

underlying the asserted utility. Nor does the Office Action demonstrate that the facts presented in the application are inconsistent with the logic underlying the assertion. The facts presented in the application are entirely consistent with the disclosed utilities for the claims.

The Examiner's statement that the asserted utility would not be apparent to one of ordinary skill in the art is completely unsupported. The Office Action does not provide "documentary evidence...to support the factual basis for the *prima facie* showing of no specific and substantial credible utility." Utility Examination Guidelines, Federal Register Notices, 66(4): 1098 (2001). The Office Action provides only a naked assertion that Applicants' disclosed homology is not sufficient to establish utility. This does not satisfy the Examiner's burden to show that "it is more likely than not that a person of ordinary skill in the art would not consider that any Utility asserted by the Applicant would be specific and substantial." Utility Examination Guidelines, p. 1098 (emphasis added). The Examiner is also reminded that

> a *prima facie* showing must contain the following elements: 1. An explanation that clearly sets forth the reasoning [for the lack of utility rejection]; 2. Support for factual findings relied upon in reaching the conclusion [of no credible, specific and substantial utility]; and 3. An evaluation of all relevant evidence of record including the closest prior art. *Id.*

The current rejection fails on at least elements 2 and 3: to wit, the Office Action cites no support whatsoever for the factual findings, if any, relied upon, and does not adequately account for all evidence of record in the application and the prior art.

In contrast to utter paucity of factual support for the Examiner's position in the Office Action, Applicants' specification provides at least two independent lines of evidence for the asserted utilities. First, Applicants note the fact that the message encoding the claimed protein is expressed in the AGM region of the developing embryo, which is a region associated with long-term repopulating (LTR) hematopoietic stem cell activity. See current specification, p.1, lines 13-20, p. 2, lines 11-12. Second, Applicants present ample evidence that the claimed protein has significant homology to the TSG protein, which the Examiner concedes has a number of well-known biological activities, i.e., interactions with BMP proteins and a role in the development of hematopoietic cell lines. Office Action paper, p.3. The Examiner provides no evidence disputing the origin of the mRNA isolated by Applicants, nor Applicants'

characterization of this region as the origin of LTR hematopoietic cells, nor the significance of the claimed protein's homology to TSG protein.

Reference (AF) listed on the enclosed Form PTO-1449 (Form 1449), Graf et al., explicitly contradicts the Office Action's assertion that a skilled artisan would not recognize as significant the disclosed homology of the claimed protein to *Drosophila* Tsg. This reference states that Tsg homologs, including mouse and *Xenopus* Tsg homologs:

> "...encode vertebrate proteins that are closely related (40% identical and >50% similar) to the *Drosophila* gene product. Shared features ...indicate that Tsg has been conserved as a secreted protein of defined secondary structure over large evolutionary distance. ....The evolutionary conservation of the Tsg protein reflects conserved interaction with DPP/BMP, while more persistent expression may indicate the acquisition of additional TSG function in mammals...
>
> ....The evolutionary conservation of the functional and biochemical interaction between tsg and dpp/BMP, places Tsg in the BMP pathway." Graf et al., p.558 right hand column, first and second paragraphs (citations omitted) (emphasis added).

Furthermore, Graf et al. and other references submitted with the enclosed Form 1449 validate several of Applicants' asserted utilities. First, some of these references confirm that TSG is useful as a regulator of BMP activity by interacting with BMP2/4. See, e.g., Nosaka et al. Abstract, lines 8-9, disclosing that TSG acts as "a BMP-4 agonist in skeletogenesis." See also the passage quoted above from Graf et al., p.558, and also Chang et al., (Ref. AG) p.484, second paragraph, right hand column and Figure 4.

Second, Nosaka et al. and Graf et al. both confirm that the nucleotide sequences disclosed in the present application can be used as probes to study TSG expression during embryonic and post-embryonic development or to study the tissue distribution of TSG expression. See Nosaka et al., Figures 1, 2 and 3; and Graf et al., Figures 2, 3, and 4.

Third, Chang et al. confirms that skilled artisans did recognize that the FLAG-TSG fusion proteins disclosed by Applicants (e.g., at p.5 line 25-p.6 line 10, of the present specification) are useful for purifying and identifying proteins related to hematopoietic stem cell formation and bone formation. See Chang et al., Figure 4b, and p.486, left hand column, first

paragraph, showing that anti-FLAG antibodies coimmunoprecipate a ternary complex of FLAG-TSG, BMP and chordin.

Fourth, Chang et al. describes the use of mouse and other vertebrate TSG mRNAs to study the mechanisms of development of hematopoietic derived tissues, e.g., blood and bones (but not mesodermal tissues), thus supporting an asserted utility of the claimed nucleic acids. Chang et al., p. 483, right hand column, Fig. 1, Fig. 2, and p.484, the paragraph starting in right hand column (indicating that similar phenotypes were induced by use of different vertebrate TSG mRNAs).

Fifth, the Nosaka et al., reference strikingly bears out a number of Applicants' asserted biological functions for the proteins and nucleic acids of the present invention, e.g., that mammalian TSG participates in bone formation and in the development of long-term repopulating hematopoietic stem cell-derived tissues. The knock-out mice constructed by Nosaka et al. display distinct dwarfism and "kinky-tail" phenotypes. See Nosaka et al., Figures 4-9. These knock-out mice also develop distinct phenotypes in lymphatic tissues such as blood, spleen, and thymus. See Nosaka et al., Figures 11, 12 and 13.

The post–filing date reports provided by Applicants confirm that the utilities asserted in the specification are specific and substantial, "real-world" utilities that would have been (since, in fact, they were) considered credible by skilled artisans. These references also directly contradict the Examiner's unsupported assertion that the disclosed homology of mammalian TSG "is not sufficient to identify it as having similar properties" to *Drosophila* Tsg, as all three references discussed above show that persons of skill in the art did in fact consider the homology between mammalian TSG and *Drosophila* Tsg to be significant and indicative of conserved biological function.

Applicants respectfully submit that the Examiner has not even begun to establish a *prima facie* case that the present application fails to assert a specific and substantial credible utility.

Finally, Applicants submit that a person of ordinary skill in the art would recognize at least one well-established utility for the disclosed TSG-like nucleotide sequences: the generation

of TSG knock-out mice. Methods for generating knock-out mice were, of course, known in the prior art. The TSG protein's homology to *Drosophila* Tsg, the interaction of *Drosophila* Tsg with the *Drosophila* homolog of mammalian BMP2/4, the recognized role of BMP2/4 in bone formation and hematopoietic stem cell derived tissues, and the fact that the gene is clearly expressed during embryonic development in tissues known to be the source of persistent long-term repopulating hematopoietic stem cells (the AGM), as well as in other identified tissues (specification p.1, lines 13-20; p. 2, lines 11-12; and Example 3), all provided a person of ordinary skill in the art with ample basis to believe the nucleic acids disclosed in the present invention would be useful as starting materials to generate TSG knock-out mice. Nosaka et al. confirms that persons of skill in the art did recognize the utility of such knock-out mice as a tool for studying bone formation and hematopoietic stem cell-line derived tissues. This is therefore a "well-established" utility that, independent of the asserted utilities, satisfies the utility requirement.

For the reasons disclosed above, Applicants respectfully request that the rejection for lack of utility be withdrawn.

**35 U.S.C. § 112, First Paragraph, Enablement**

Claims 1-10, 13, 14, and 17 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement because of the alleged lack of utility. Applicants respectfully traverse this rejection as it may apply to all amended claims, for the reasons stated above, i.e., Applicants submit that they have asserted multiple specific, substantial, and credible utilities, and in addition have described a well-asserted utility, for the claimed subject matter.

Applicants also remind the Examiner that mere lack of objective data does not mean that the specification is not enabling; indeed, many valid claims issue based upon nothing more than a constructive reduction to practice. As stated in *In re Armbruster*, 185 USPQ 152, 154 (CCPA 1975),

> As a matter of Patent Office practice...a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used

> in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. (emphasis in original)

The Office Action does not supply any reason to doubt the objective truth of the asserted utilities contained in the specification. ***If the Examiner intends to maintain this rejection, it is essential that she explicitly set forth her reason to doubt the objective truth of the statements contained in the specification so that Applicant can respond appropriately.*** Merely opining that the field is generally unpredictable or that the specification has not provided sufficient evidence does not tell Applicant *why* the Examiner "doubts the objective truth" of statements contained in the specification, nor even *what* statements are doubted. Without that insight, it is difficult to respond.

Becauses this enablement rejection is premised solely on an alleged lack of utility for the disclosed invention, Applicants do not repeat the discussion above that details multiple asserted utilities and a well-established utility for the present invention. Applicants only reiterate that the Office Action improperly fails to provide <u>any</u> evidence that would support the rejections under 35 U.S.C. §§ 101 and 112, based on an alleged lack of utility.

Furthermore, the post-filing publications supplied with the enclosed Information Disclosure Statement provide additional documentary proofs that the current specification enables one of ordinary skill to practice an invention that would have been recognized as useful for each of several purposes. Regarding this point, the *Armbruster* court stated at 153:

> Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; <u>such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling</u>.
>
> ... <u>it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement</u>. Otherwise, there would be no need for the

> Applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. (emphasis added)

Even though the Office Action does not meet the initial burden of establishing that there exists a sufficient reason to doubt the objective truth of statements in the specification, Applicants have supplied new documentary evidence demonstrating that persons of skill in the art would have recognized the invention as useful.

For the reasons presented above, Applicants respectfully request that this rejection, and the tandem rejection based on 35 U.S.C. §101, be withdrawn as to all claims.

The Examiner also rejected claims 1-3, 5-10, 13, 14, and 17 because the specification allegedly fails to enable the claimed variants and fragments of the nucleotide sequences. The rejection further argues that because "the biological function, activity, or essential properties of the TSG-like gene are not...specified, thus there is no meaning to the limitation 'functionally equivalent'." Office Action paper, p.4-5. Applicants respectfully traverse this rejection as it may apply to the amended claims.

As an initial matter, Applicants point out that, contrary to the Office Action's assertion, the present specification does define "functionally equivalent":

> In the present invention, the term "functionally equivalent" means that the target protein has an activity for rescuing aberrations in the differentiation of dorsal midline cells when injected into a TSG mutant of Drosophila, or an activity that regulates embryo development (for example, dorsoventral induction capability) when injected into Xenopus eggs. In addition, the protein of the present invention is also suggested to have the function of promoting the signaling activity of BMP (bone morphogenetic protein; DPP) by binding with BMP.... p.4, lines 23-29.

Thus, the disclosure provides three specific assays for TSG function: i) rescue of the developmental dorsal midline phenotypes in TSG Drosophila mutants, ii) promoting BMP signaling and iii) BMP binding. Assays for all three functions are known in the art (see e.g., p.2, lines 7-9) thereby enabling skilled artisans to assess the functional equivalence of claimed variants. Nevertheless, in an effort to move the case to allowance, Applicants have amended the claims as described below.

Claim 1 has been amended so that it no longer recites "fragments" or "variants" of the claimed nucleotide sequences, thereby obviating this aspect of Examiner's rejection for claim 1 and dependent claims 5, 7, 9, and 13.

The subject matter of parts (c) and (e) of original claim 1 has been narrowed and transferred to new claims 44 and 46, respectively. New claim 44 recites an isolated nucleic acid encoding a protein that comprises SEQ ID NO:2 in which "15 or fewer amino acids are substituted, deleted, and/or inserted", and that binds BMP2/4. New claim 46 recites an isolated nucleic acid encoding a protein with at least 90% identity to SEQ ID NO:2 and that binds BMP2/4. Claim 2 has been amended to require the fragment to be at least 40% of the length of SEQ ID NO:2 and to have the function of binding BMP2/4.

The amended claims directed to nucleotide sequence variants, i.e., claims 2, 3, 6, 8, 10, 14, are amended to narrow their scope and explicitly recite a function: binding BMP2/4. Sufficient structural and functional limitations are recited by the amended claims (and new claims) to enable a skilled artisan, in light of the specification, to practice the claimed subject matter without undue experimentation.

Claim 17 has been amended to recite the conditions for hybridization. Thus, sufficient structural and functional details are recited by the currently amended claim to enable a skilled artisan to practice the claimed subject matter without undue experimentation.

For the reasons presented above, Applicants respectfully request that this rejection be withdrawn.

**35 U.S.C. § 112, First Paragraph, Written Description**

Claims 1-3, 5-10, 13, 14, and 17 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking sufficient written description. The Examiner states that because only one species is disclosed, an insufficient number of species are disclosed to support the genus of any polynucleotide encoding sequences related to SEQ ID NO:2. Applicants respectfully traverse this rejection as it may apply to the presently amended claims.

The specification discloses both structural and functional features that describe the currently claimed genera of nucleic acids. Claim 1 has been amended to no longer include reference to nucleic acids that encode "variants" of SEQ ID NO:2, thereby obviating this rejection as to claim 1 and dependent claims 5, 7, 9, and 13.

Many of the variants originally claimed by claim 1 are now encompassed by new claims 44-49. The new claims specify nucleic acids encoding proteins that are highly (i.e., at least 90%) identical to SEQ ID NO:2 and that bind BMP2/4. These new claims have a scope that the the Written Description guideline training materials indicate is sufficient to satisfy the statutory written description requirement. Example 14 on p.53 of the Written Description guideline training materials clarifies that claims that are directed to a genus of sequences with a high degree of identity to a disclosed sequence and that recite a biological activity are sufficiently described by the actual reduction to practice of a single sequence species. Therefore, the subject matter of new claims 44-49 was clearly sufficiently described so as to convey to a skilled artisan that the inventors had possession of the claimed genus.

Figure 1 of the application provides an alignment of SEQ ID NO:2 with the relevant *Drosophila* Tsg protein. The alignment provides a wealth of information about conserved regions that would be apparent to a skilled artisan. The conserved regions are especially notable given the phylogenically distant relationship between fruit flies and mice. One striking feature revealed by the alignment is the conservation of all 24 cysteine residues outside the signal sequence (the first 24 residues) of SEQ ID NO:2. Also apparent is the very high degree of sequence homology in conserved regions of SEQ ID NO:2. For example, of the first 52 residues following the signal sequence (amino acids 25-76), 28 residues are identical to their counterparts in *Drosophila* and a total of 44 residues are homologous. Even more striking is the region between residues 184 and 204 of SEQ ID NO:2, where 17 of 21 residues are identical and the remaining four residues are homologous to the *Drosophila* protein. The Examiner has not explained why these readily apparent features of Figure 1 do not count as a "description of the conserved regions which are critical to the structure and function of the genus claimed." One of ordinary skill in the art seeking to produce biologically active variants of SEQ ID NO:2 would

know to make few or only conservative substitutions within the conserved regions revealed by Figure 1, and would understand that the cysteine residues are likely to play a critical role.

Claim 2 has been amended to recite fragments that are at least 40% of SEQ ID NO:2 and that bind BMP 2/4. The appropriate standard is whether a skilled artisan would conclude from reading the disclosure that Applicants were in possession of the claimed genus, i.e., whether Applicants recognized and described the necessary common attributes possessed by the claimed genus. The present specification discloses SEQ ID NO:2, the requirement that the claimed fragments include at least 40% of SEQ ID NO:2, and the limitation that the fragments must be able to bind BMP 2/4. A person of ordinary skill would conclude from reading the disclosure that Applicants had recognized and described the necessary and common attributes of the fragments claimed by amended claim 2, and its dependent claims 6, 8, 10, and 14.

Claim 17 has been amended to recite the conditions under which the claimed nucleic acid hybridizes to SEQ ID NO:1 or its complementary strand. Therefore, claim 17 contains sufficient structural and functional limitations to satisfy the Written Description requirement of 35 U.S.C. §112, first paragraph. See, e.g., Example 9 on pp. 35-37 of the Written Description guideline training materials.

For the reasons presented above, Applicants respectfully request that this rejection be withdrawn.

**35 U.S.C. § 112, Second Paragraph, Indefiniteness**

Claims 1, 3-5, 7, and 9 stand rejected as allegedly indefinite. This rejection is directed to three independent features of the claims: first, the recitation of nucleic acids identified by their capacity to hybridize under stringent conditions without defining stringent conditions; second, the recitation of molecules that are functionally equivalent to the protein described by SEQ ID NO:1; and third, the recitation of molecules that hybridize with SEQ ID NO:1 and encode a protein functionally equivalent to SEQ ID NO:2.

Applicants respectfully traverse the contention that a skilled artisan would not know which conditions constitute stringent hybridization conditions. The specification provides a clear

example of stringent hybridization conditions on p.6, lines 26-30. Nevertheless, to expedite prosecution, Applicants have removed the hybridization language from claim 1, thereby rendering the rejection moot. New claim 45, directed to the subject matter of original claim 1(d), recites specific hybridization conditions. (Although not rejected on this ground, claim 17 has been similarly amended).

Applicants do not understand the following comment on p.7 of the Office Action paper:

> These claims are also indefinite in the recitation of "functionally equivalent." No function for the SEQ ID NO:1 is defined and one of skill in the art would thus not know what molecules were functionally equivalent to it.

Applicants first note for the record that none of the claims mentioned functional equivalence in the context of SEQ ID NO:1 (the nucleic acid sequence), as implied by the above-quoted statement. Rather, all the claims that mentioned functional equivalence did so in the context of SEQ ID NO:2 (the protein sequence). Second, the specification defines "functionally equivalent" on p.4, lines 23-29, making it very clear what is meant by this term. Nevertheless, Applicants have chosen to remove this language from the claims, rendering the rejection moot.

New claim 45, which incorporates the subject matter of original claim 1(d), recites a nucleic acid encoding a protein that binds BMP2/4, wherein the complement of the nucleic acid hybridizes with a probe consisting of the coding sequence of SEQ ID NO:1. This new claim language no longer covers a nucleic acid that is "the antisense" of SEQ ID NO:1 and encodes a protein that is functionally equivalent to SEQ ID NO:2.

For the reasons presented above, Applicants respectfully request that this rejection be withdrawn.

**35 U.S.C. § 102(b), Anticipation**

Claims 1, 2, 5-10, 13, 14 and 17 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by US Pat. No. 6,008,022 (the '022 patent). The Office Action states "The '022 patent teaches SEQ ID NO:1, which contains regions of >80% similarity and would hybridize under stringent conditions. See sequence alignment attached to document. It further encodes 'a fragment' of SEQ ID NO:2; no fragment size is specified." Claim 17 is rejected as anticipated

because it allegedly fails to recite hybridization conditions for the claimed nucleic acid and therefore, according the Office Action, reads on any nucleic acid, including those disclosed in the '022 patent.

As an initial matter, Applicants note that the '022 patent is not 102(b) (or 102(a)) prior art because the '022 patent issued in December 1999, which is after the priority date of September 6, 1999, claimed for the present application. Additionally, Applicants provide reasons below why this reference should not be considered an anticipating reference under any other provision of 35 U.S.C. § 102.

Claim 1, as amended, is limited to a nucleic acid encoding a protein comprising the amino acid sequence of SEQ ID NO:2. Such a nucleic acid is not disclosed by the '022 patent. Therefore, Applicants respectfully request that this rejection be withdrawn as to amended claim 1 and dependent claims 5, 7, 9 and 13.

Claim 2, as amended, recites an isolated nucleic acid encoding a fragment of SEQ ID NO:2 that is at least 40% of the length of SEQ ID NO:2 and that binds BMP2/4. SEQ ID NO:2 is a 222 amino acid sequence. SEQ ID NO:1 of the '022 patent encodes a protein with 223 amino acid residues. Since a 223 residue polypeptide cannot be fragment of a 222 residue polypeptide, Applicants respectfully request that this rejection be withdrawn as to claim 2 and dependent claims 6, 8, 10, and 14.

Claim 17 has been amended to claim polynucleotides that hybridize with the coding sequence of SEQ ID NO:1, or its complement, under specified stringency conditions. The Examiner does not point to any teaching in the '022 patent that the '022 patent SEQ ID NO:1 sequence will bind to the complement of presently disclosed SEQ ID NO:1 under such conditions. Therefore, the '022 patent does not expressly anticipate claim 17, and Applicants respectfully request that this rejection be withdrawn.

If the rejection (implicitly) relies on an inherent property of '022 patent SEQ ID NO:1, Applicants point out that the Examiner has failed to provide "a basis in fact and/or a technical reason to support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP 2112 quoting Ex parte Levy, 17 USPQ2d

1461, 1464 (B.P.A.I. 1990). "To establish inherency the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency...may not be established by possibilities or probabilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" In re Robertson, 169 f.3d 743, 745 (Fed. Cir. 1999)(citations omitted). The Examiner has provided no basis for concluding that a person of ordinary skill in the art, would upon inspecting the '022 sequence, conclude that it necessarily hybridizes under the stringent conditions recited in amended claim 17. For these reasons Applicants respectfully request that this rejection be withdrawn as to claim 17.

New claim 45 is directed to the subject matter of original claim 1(d). Claim 45 recites a nucleic acid (a) that encodes a protein that binds to BMP2/4 and (b) whose complement hybridizes with the coding sequence of SEQ ID NO:1 under specified hybridization conditions. For the same reasons given above for claim 17, the '022 patent SEQ ID NO:1 does not anticipate the presently claimed subject matter. Furthermore, the '022 patent nowhere discloses a nucleic acid encoding a protein that binds BMP2/4.

For the reasons presented above, Applicants respectfully request that this rejection be withdrawn as to all claims.

Enclosed is a $994.00 check for excess claim fees and a $180 check for Submission of an Information Disclosure Statement fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: April 22, 2004

Marcos P. Rivas
Reg. No. 54,401
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